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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,742	12/28/2001	James G. Karras	ISPH-0623	8407

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 12/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/033,742	Applicant(s) KARRAS ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 15-20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Restriction Requirement filed October 2, 2002, in Paper No. 6.

Claims 1-20 are pending in the instant application.

Claims 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claims 1-14 have been examined as indicated below.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14) in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of MIP-3α. Further, Applicant argues that a search of literature relating to MIP-3 α would clearly reveal art relating to all of the claims, and therefore would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 6), the compound of Group I may be used in another method other than the method of Group II. Therefore, a search for the compound of Group I will not encompass all of the art relevant to the method of Group II. With regard to the relationship of the claims as product, process of making and process of using, the argument is not persuasive because restriction is proper regardless of whether the claims are related as product and process of making or product, process of making and process of using. Where claims are drawn to a product, process of making and process of using, restriction may be required where

the process of making and product made are distinct according to the guidelines set forth in MPEP 806.05(f) (see MPEP 806.05(i)), as was demonstrated for the product and process of using of the instant application.

Applicant's election of SEQ ID NO:3 with traverse in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the identified antisense sequences recited share the ability to modulate a common structure, namely human MIP-3α and are therefore not patentably distinct. This is not found persuasive because, as argued in the restriction requirement (Paper No. 6), pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, up to 10 independent and distinct nucleotide sequences will be examined in a single application (see MPEP 803.04 and 2434). Furthermore, as argued in the restriction requirement, each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of MIP-3 α, and each antisense, upon binding to MIP-3 α, functionally modulates (increases or decreases) the expression of the gene to a varying degree (per applicant's Table 1 in the specification). These independent antisense sequences are therefore distinct. Further, as stated in the restriction requirement, a search of more than one (1) of the antisense sequences claimed presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences.

The requirement is still deemed proper and is therefore made FINAL.

Nucleotide and/or Amino Acid Sequence Disclosure

This application contains sequence disclosures (see SEQ ID NO: 32) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R.

§1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Please see attached Notice to Comply with Sequence Rules and marked up Raw Sequence Listing sheet. Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102 (a) as being anticipated by Schlegel et al. [WO/01/42467].

Claims 1 and 2 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding MIP-3 α (SEQ ID NO:3); wherein said compound specifically hybridizes with the nucleic acid molecule encoding MIP-3 α and inhibits the expression of MIP-3 α; wherein the compound is an antisense. Claim 11 is drawn to a compound 8 to 50 nucleobases in length that specifically hybridizes with at least an 8-nucleobase portion of a preferred target region on a nucleic acid encoding MIP-3 α (SEQ ID NO:3).

The specification at page 6, lines 26-30 recite, "Disclosed and claimed in PCT Publication WO 01/142467 is an isolated nucleic acid molecule which is at least 90% homologous to human macrophage inflammatory protein 3-alpha or a fragment or complement thereof, which can hybridize to macrophage inflammatory protein 3-alpha under conditions of moderate or high stringency" (also see '467 page 14, lines 16-23). Schlegel et al. ('467) further disclose the expression of a marker listed within Tables 1-4 (note, an isolated nucleic acid molecule which is at least 90% homologous to human macrophage inflammatory protein 3-alpha (MIP-3 α) is contained within Tables 1-4) can be inhibited by an antisense oligonucleotide (see page 26, lines 13-16). Schlegel et al. further disclose the isolated nucleic acid molecule is at least 7 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid corresponding to a marker (note, an isolated nucleic acid molecule which is at least 90% homologous to human macrophage inflammatory protein 3-alpha (MIP-3 α) is a marker) or a nucleic acid encoding a protein corresponding to a marker (see page 32, lines 24-29).

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102 (b) as being anticipated by Hromas, R. [U.S. Patent No. 6,096,300].

Hromas, R. discloses a human macrophage inflammatory protein 3-alpha (MIP-3 α) nucleotide and protein sequence (see SEQ ID NOs: 1 and 2, respectively). Hromas, R. disclosure of SEQ ID NO: 1 is identical to SEQ ID NO: 3 of the instant invention. Hromas, R. further discloses purified and isolated polynucleotides (i.e. DNA and RNA, both sense and antisense strands encoding Exodus (human macrophage inflammatory protein 3-alpha)) (see column 6, lines 27-31). Hromas, R. further discloses a purified polynucleotide which hybridizes

under stringent conditions to the complementary strand of the Exodus coding portion of the DNA of SEQ ID NO: 1 (see column 6-7 lines 66-68 and 1-16, respectively).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlegel et al. [WO/01/42467] and Hromas, R. [U.S. Patent No. 6,096,300] in further view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1-10 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding macrophage inflammatory protein 3-alpha (MIP-3α); wherein said compound specifically hybridizes with the nucleic acid molecule encoding (MIP-3α) and inhibits the expression of (MIP-3α); wherein the compound is an antisense; wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 10-14 are drawn to a composition comprising the compound

8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding (MIP-3α) and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Schlegel et al. [WO/01/42467] and Hromas, R. [U.S. Patent No. 6,096,300] are relied upon as cited in the 102 rejection above.

Schlegel et al. [WO/01/42467] and Hromas, R. [U.S. Patent No. 6,096,300] do not teach wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding MIP-3α and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to target and inhibit the expression of macrophage inflammatory protein 3-alpha (MIP-3α) because the prior art has taught antisense oligonucleotides complementary to MIP-3α can inhibit MIP-3α expression (Schlegel et al. and Hromas, R.). One of ordinary skill in the art would have been motivated to inhibit the expression of MIP-3α since the prior art has taught that Exodus (MIP-3α) is a chemokine that regulates mononuclear chemotaxis (see Hromas, R. (Figure 1)). One of ordinary skill in the art would have expected success in making a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding MIP-3α; wherein said compound specifically hybridizes with the nucleic acid molecule encoding MIP-3α and inhibits the expression of MIP-3α since the prior art has taught a nucleic acid, 7 or more nucleotides in length, can hybridize under stringent conditions to a nucleic acid corresponding to a marker, wherein the marker is a nucleic acid molecule which is at least 90% homologous to human macrophage inflammatory protein 3-alpha or a fragment or complement thereof (see Schlegel et al.). One of ordinary skill in the art would have been motivated to modify antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal

stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

It would have been obvious to one of ordinary skill in the art, at the time of filing, to combine the teachings of Schlegel et al. and Hromas, R. with the methods of Baracchini et al. and Fritz et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful since Schlegel et al. and Hromas, R. nucleic acid molecules that hybridize to macrophage inflammatory protein 3-alpha (MIP-3α) under conditions of moderate or high stringency to inhibit MIP-3α expression and since Baracchini et al. and Fritz et al. taught the successful use of modified antisense oligonucleotides enhance affinity for nucleic acid target and exhibit high colloidal stability with low side effects.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable because they are not free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
December 17, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635